

**Conclusion:** Reduced BMD and minimal trauma fractures are both features of HIES, but the degree of osteopenia does not correlate with fractures, nor is there laboratory evidence of increased bone turnover.

## 05

### HIV Treatment Induced Hypogammaglobulinemia – Unmasked Common Variable Immune Deficiency (CVID)

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**Background:** CVID is a very heterogeneous syndrome that is characterized by low immunoglobulin production, impaired specific antibody responses to pathogens, recurrent bacterial infections, autoimmune abnormalities and splenomegaly. Causes for CVID include: failure of B cell maturation, altered somatic hypermutation, defective cell membrane signaling, T cell abnormalities, reduced CD40 ligand expression, inducible co-stimulator protein (ICOS), and L-selectin and defects in tumor necrosis factor receptor super family members. HIV infection induces abnormalities intrinsic to B cells including hypergammaglobulinemia, increases autoantibody levels, activation markers and risk for B cell lymphoma. Despite the polyclonal hypergammaglobulinemia, paradoxically HIV infection results in poor specific antibody responsiveness to vaccination. In the world literature, 4 patients with CVID have been reported that have had a reversal of hypogammaglobulinemia and improved antibody production as a result of HIV infection. We describe a fifth such patient whose antibody production was normal while infected with HIV yet declined as a result of antiretroviral therapy (ART).

**Objective:** To describe how HIV therapy unmasked hypogammaglobulinemia in this patient with HIV and CVID.

**Method:** The Immune Deficiency Treatment Centre (IDTC) actively follows more than 700 persons with HIV and 45 with CVID. One person has both HIV and CVID. Paradoxically the patient was well and asymptomatic prior to beginning potent ART. Within 2 weeks of beginning treatment, his immunoglobulin levels fell dramatically and he developed bacterial pneumonia and diarrhea.

**Results:** In addition to low immunoglobulin serum levels, the patient had a B cell phenotype consistent with almost no memory B cells. The impact of HIV therapy is shown in the table.

Treatment	NONE			ART		
				IVIG		
Date	04/2004	08/2004	06/2005	07/2005	09/2005	12/2005
HIV-1 RNA copies/ml	111,000	107,800	175,000	976	<50	<50
CD4 cells/mm <sup>3</sup>	407	290	100	130	96	225
IgG (range 7–18 g/L)		7.20	5.26	3.92	8.98	8.90
IgA (range 0.7–5.0 g/L)		1.10	1.10	0.51	0.53	0.53
IgM (range 0.4–2.4 g/L)		0.55	0.55	<0.24	<0.24	<0.24

**Conclusion:** Understanding the recovery of antibody production in a patient with CVID as a result of HIV infection, or the loss of immunoglobulin production in HIV infected patients with CVID who begin ART, may lead to the identification of factors important in the pathogenesis of CVID. Studies of viral and immune factors in this patient are being initiated.

## 06

### Novel TTF1 Mutation in a Patient with Hypothyroidism, Chorea and Mild IgA Deficiency

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**Background:** Congenital hypothyroidism is caused by developmental defects of the thyroid gland. Associated neurological symptoms are due to the lack of thyroid hormone in the developing brain. Here, we report a 34-year-old Caucasian woman with recurrent bronchitis, a lifelong history of "clumsiness" and "ataxia" without cognitive developmental delay. She had been diagnosed with hypothyroidism, and had been variously characterized as having truncal ataxia, myoclonic dystonia, and factitious movement disorder. Previous evaluation had shown a mildly diminished IgA (60% of the lower limit of normal), but normal IgG and IgM. IgE was not elevated.

**History:** The family history was remarkable. Her paternal grandfather had had "ataxia" and mild speech delay. Her father had had "clumsiness" starting in childhood with a right foot drop. Her 39-year-old brother was oxygen dependent due to severe pulmonary fibrosis, recurrent pneumonias and a similar neurological disorder. Her fraternal twin sister had a similar early onset neurological disorder and died of staphylococcal sepsis following Caesarean section delivery of a baby girl. The daughter of her deceased sister had the same neurological disorder with onset in infancy. All affected adults had hypothyroidism and low IgA levels, similar to the index patient. In view of the familial constellation of neurologic disorder, hypothyroidism, and pulmonary fibrosis, we looked for mutations in thyroid transcription factor 1 (TTF-1, TITF1, Nkx2.1). TTF1 is an epithelial